PSYCHOPHYSIOLOGY OF POSTPARTUM DEPRESSION

CHANGES IN MATERNAL PSYCHOPHYSIOLOGY OCCURRING IN RESPONSE TO PEER-DELIVERED COGNITIVE BEHAVIORAL THERAPY FOR POSTPARTUM DEPRESSION

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TITLE: Changes in Maternal Psychophysiology Occurring in Response to Peer-Delivered Cognitive Behavioral Therapy for Postpartum Depression

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Lay Abstract

Postpartum depression affects up to one in five mothers in the first year after delivery. When treated promptly with talking therapies (i.e., psychotherapy) such as cognitive behavioural therapy (CBT), many experience significant improvements in their symptoms. However, the changes occurring in the brain and the remainder of the nervous system occurring in response to psychotherapy is not well known. It is important that this is understood so that we can develop more effective treatments and better predict who will respond to different types of treatments. In particular, the role of the frontal lobe of the brain, and the body's parasympathetic system is poorly understood in the context of PPD. This thesis aimed to examine the impact of CBT on women's frontal lobe functioning using a measure called frontal alpha asymmetry (FAA) measured via electroencephalography (EEG), and parasympathetic nervous system-based heart rate variability (HRV) using electrocardiography (ECG). In this study, we compared mothers with PPD treated with CBT to those who did not receive this treatment. We found that HRV responded in mothers who received CBT compared to women who were in the control group. No significant changes were found for FAA after treatment. These results suggest that HRV may be explored further as a valid treatment outcome for CBT when provided to women with PPD.

Abstract

Background: Postpartum Depression (PPD) affects up to one in five mothers. While psychotherapy can effectively reduce symptoms of PPD, it is unclear how PPD treatment affects maternal psychophysiology. Determining physiological changes in response to cognitive behavioural therapy (CBT) could provide insights into the mechanisms underlying effective treatment and/or help predict treatment outcomes. This study examined if treating PPD with CBT led to changes in frontal cortical activity and heart rate variability, two markers of maternal emotion regulatory capacity.

Methods: Community-dwelling mothers with PPD (Edinburgh Postnatal Depression Scores ≥10) were randomized to receive nine weeks of group CBT delivered by recovered peers (i.e., those who had previously recovered from PPD) (n=26) or be put on a waitlist to receive the intervention nine weeks later (n=24). Electroencephalographic (frontal alpha asymmetry), electrocardiographic (heart rate variability), and clinical (depression, anxiety) data were collected at baseline and nine weeks later.

Results: Participants in both the immediate treatment and waitlist control groups reported moderate levels of depression and anxiety at baseline. After treatment, mothers in the treatment group showed greater improvements in depression ($p<0.01$, Cohen d=1.22), and anxiety ($p<0.005$, Cohen d = 1.48), and high-frequency heart rate variability ($p<0.05$, Cohen d=0.70), but not frontal alpha asymmetry, compared to the waitlist control group.

Conclusion: Group CBT for PPD can improve symptoms of depression and anxiety and parasympathetic nervous system function. Future research should attempt to replicate and extend these findings using larger samples, additional biomarkers, and longer periods of follow up.

Examining how evidence-based treatments for PPD affect maternal psychophysiology can improve our understanding and potentially predict treatment effects.

Keywords: Postpartum depression, cognitive behavioural therapy, physiology, frontal alpha asymmetry, heart rate variability.

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List of All Abbreviations

ANS - Autonomic Nervous System

CBT - Cognitive Behavioural Therapy

CI - Confidence Interval

DVC - Dorsal Vagal Complex

ECG - Electrocardiogram

EEG -Electroencephalogram

EPDS - Edinburgh Postnatal Depression Scale

FAA - Frontal Alpha Asymmetry

GAD - Generalized Anxiety Disorder

HF-HRV - High Frequency Heart Rate Variability

LMM - Linear Mixed-effects Model

M - Mean

MINI - Mini International Neuropsychiatric Interview

N - Number of participants

PNS - Parasympathetic Nervous System

PPD - Postpartum Depression

RSA - Respiratory Sinus Arrhythmia

SD - Standard Deviation

SNS - Sympathetic Nervous System

SPSS - Statistical Package for the Social Sciences

T1 - Time 1

T2 - Time 2

VVC- Ventral Vagal Complex

Declaration of Academic Achievement

The thesis is presented as a standard thesis but will be prepared for a submission to a peer-reviewed journal. The contribution to this paper is described below.

Article title: Changes in Maternal Psychophysiology Occurring in Response to Peer-Delivered Cognitive Behavioral Therapy for Postpartum Depression

Authors: Tarindhya Karunagoda, Bahar Amani, John Krzeczkowski, Calan Savoy, Ryan J. Van Lieshout.

Contribution: Tarindhya Karunagoda formulated the research question, aided in participant screening and running the study sessions, collected and organized data, entered data of participants into a statistical analysis software, performed statistical analyses, and wrote the paper. Bahar Amani was involved in the design, management of the study, data collection, data analysis training, led the study sessions, edited and reviewed the paper. John Krzeczkowski also contributed to data analysis training, edited and reviewed the paper. Calan Savoy helped with the data analysis plan of the study, the statistical analyses and edited the paper. Dr. Van Lieshout conceived, guided and managed the entirety of the project. He also reviewed and edited the paper.

Introduction

Postpartum depression (PPD) affects up to one in five mothers in high-income countries and can have significant adverse consequences in both the short- and long-term (Gaynes et al., 2005; Stewart and Vigod, 2019; Payne & Mcguire, 2019). It is associated with a three to six times increased risk of future depressive episodes (Josefsso et al., 2001), and when untreated can persist in up to 24% of women at one year, and 13% at two years (Campbell and Cohn, 1997).

An understanding of the pathophysiology of PPD can not only help us better understand its causes but provide potential markers for prediction and treatment optimization. Most research in this area has been focused on understanding the basic biological processes underlying the development of PPD and has examined neuroendocrine or neuroinflammatory pathways (Buckwalter et al., 1999; Krause et al., 2014; Guintivano et al.2018). This includes but is not limited to the role of the Hypothalamic Pituitary Adrenal (HPA) axis, reproductive hormones, proinflammatory cytokines and polymorphism in transporter and receptor genes (Yim et al., 2015). Despite the involvement of the autonomic nervous system (ANS) and frontal cortical activity in the pathophysiology of major depressive disorder in general population samples (Henriques and Davidson, 1990; Rottenberg, 2007; Izumi et al., 2016; Hartmann et al., 2019), these domains have yet to be studied extensively in the context of PPD.

High-Frequency Heart Rate Variability (HF-HRV) is a commonly used marker of parasympathetic nervous system activity, measured by respiratory sinus arrhythmia (RSA), the baroreceptor reflex that mediates heart rate via the vagus nerve (Izumi et al., 2016; Shaffer and Ginsberg, 2017). Higher values of HF-HRV are associated with better regulation of ANS activity in response to external stimuli and has been linked to an individual's ability to respond to the demands of their environment (Blanck et al., 2019). Individuals with depression and/or anxiety

manifest decreased autonomic nervous system activity, specifically a low resting HF-HRV (Izumi et al., 2016, Rottenberg, 2007, Hartmann et al., 2019). Depressed and anxious mothers also displayed lower HF-HRV compared to healthy control women up to two years postpartum (Izumi et al., 2016). Consequently, when depression has been treated in general population samples, with antidepressants, HF-HRV has been shown to improve, normalizing to the levels seen in healthy controls (Hartmann et al., 2019). Despite this, it is uncertain whether HF-HRV is altered through CBT specifically in mothers with PPD, and would be a valuable avenue to explore in order to expand treatment options for PPD.

Frontal brain activity has been studied in depressed individuals outside of the perinatal period in order to understand brain activation patterns. According to the approach-withdrawal hypothesis, left frontal cortical activation is dominant for approach-type behaviours, while right frontal cortical activation is linked to withdrawal (Demaree et al., 2015). Cortical activation is measured by examining the relative alpha signal asymmetry via electroencephalography (EEG), while frontal alpha asymmetry (FAA) is the measured difference of alpha wave activity (8-12 Hz) in the frontal region of the brain. The lateralization of the frontal alpha wave activity can be used to determine the lateralization of the cortical activity in the frontal lobe as they are inversely related. Therefore, greater left frontal brain activity (greater right FAA) is associated with approach-type behaviours/emotions (e.g., approaching or engaging stimuli), and greater right frontal brain activity (greater left FAA) is associated with withdrawal-type behaviours/emotions (aversive responses) (Deldin and Chiu, 2005).

Consistent with the approach-withdrawal hypothesis, studies suggest that greater relative right frontal brain activity is associated with right frontal brain activity, as well as a shift to left frontal brain activity when those struggling with mental disorders are treated (e.g., Moscovitch et

al., 2011). However, there are some inconsistencies in the findings of studies in clinical and non-samples examining FAA as a biomarker of psychopathology (Segrave et al., 2011; Gold et al., 2013). One study revealed pre-treatment differences between depressed and healthy control adults where there was greater right lateralization in the depressed group. However, this did not change in the depressed group after a behavioural activation treatment despite decreases in depressive symptoms (Gollan et al., 2014). Most instanced of FAA being examined in the context of PPD has been in relation to its effects on infant emotion regulation (Wen et al., 2017). However, to date there remains a gap in the literature of studies that examine the psychophysiology of women with PPD, and whether the treatment affects these important biomarkers (e.g., FAA, HF-HRV).

Mothers with PPD prefer psychotherapy over medications because of concerns about the transmission of antidepressants and their metabolites through breast milk to their infants (Scope et al., 2013). Cognitive Behavioural Therapy (CBT) is an evidence-based treatment for PPD in both individual and group formats (Sockol, 2015), and is not only preferred by women but cost-effective (Tucker and Oei, 2007). Group CBT may be particularly attractive given that it can reduce wait times, improve accessibility, and provide social support (Scope et al., 2013).

Given this background, the present study examines the impact of a nine-week group CBT intervention delivered by women who have previously recovered from PPD (i.e., peers) on maternal depression, anxiety, HRV and FAA.

Methods

Sample/Participants

This study represents an analysis of the secondary objectives of a previously completed randomized controlled trial of peer-led group CBT for PPD, the primary objective of which was to examine its impact on postpartum depression and anxiety (National Library of Medicine [NLM], NCT03285139). Recruitment took place between March 2018 to February 2020 and participants were recruited from Brantford, Ontario, Canada via social media (e.g., Facebook, Instagram), our community agency partner (Kids Can Fly), as well as healthcare providers (public health nurses, midwives, family physicians). Participants were able to self-refer to the study or be referred through their healthcare provider.

Mothers were eligible for the study if they were at least 18 years of age, fluent in English, had an infant <12 months of age, an Edinburgh Postnatal Depression Scale Score (EPDS) ≥10, and were free of bipolar disorder, psychotic disorder, and substance use disorder as per the Mini-International Neuropsychiatric Interview (MINI). The study received approval for ethics from the Hamilton Integrated Research Ethics Board and informed consent was received from the participants before study initiation.

Intervention

At enrollment, a research assistant randomized participants in a 1:1 ratio to the experimental or waitlist control group. The experimental group received a nine-week group CBT for PPD intervention at a community centre delivered by two randomly assigned peer facilitators, in addition to treatment as usual (TAU) from their healthcare providers (family physician, midwife, private therapist, etc.). In Ontario, Canada, healthcare is universally available indicating that TAU may involve medications and/or psychotherapy from a physician and/or

clinician at a provincially funded facility/program. Private therapists or any other complementary and alternative treatments were also permitted to be accessed. The waitlist control group received TAU plus the intervention nine weeks after enrollment.

Peer facilitators were women who had experienced and recovered from PPD were and were currently free of current mood and anxiety disorders (below clinical cut-offs on the Beck Depression Inventory-II and the Generalized Anxiety Disorder-7 (GAD-7) scale) (Beck et al., 1996; Spitzer et al., 2006). Peer facilitators received two days of in-classroom instruction from a perinatal psychiatrist, observed expert therapists deliver the nine-week group in the hospital setting in which it was developed, and then delivered their own digitally recorded groups. Peer facilitators received one hour of psychotherapy supervision after each weekly session.

Data Collection

All data were collected from both groups at baseline (T1) and nine weeks later (T2). Upon enrolling in the study, women completed self-report questionnaires and attended an in-person study visit (T1) where psychophysiological data were collected during a resting-state baseline task. Mothers sat with their infants in their laps and were asked not to move or speak while they looked towards a neutral screensaver on a laptop together. This recording was 6 minutes in duration. The procedure was repeated nine weeks later (T2) for both groups. Study visits took place in the same centrally located community centre as the intervention.

Outcome Measures

High-Frequency Heart Rate Variability: Resting-state HRV data were obtained from mothers using the ECG system of Mindware Technologies Ltd version 3.2.3. (Westerville, OH). Prior to recording, ECG leads were placed on the area of the right clavicle and the 10th left and right rib. Signals were collected and transmitted to a Mindware Mobile Unit which transmitted to

a laptop in an adjacent room. Once six minutes of data were recorded, the ECG signal was analyzed using the Mindware Technologies Heart Rate Variability Analysis version 3.2.5 software. A Frequency Domain Analysis was conducted where the power within the 0.150 - 0.400 Hz was extracted from the ECG signal (Thayer and Lane, 2007). ECG data were analyzed in time frames of 60-second epochs with a target HF-HRV range of 2-8. Artifact errors were manually adjusted if there was an error in identifying an R peak. The values from five minutes of recording were then averaged to calculate the average baseline HF-HRV.

Frontal Alpha Asymmetry: EEG recordings were acquired using the InteraXon Muse™ (Ontario, Canada) headset consisting of 4 channels (AF7, AF8, TP9, TP10) and one reference electrode, Fpz. These headsets were utilized because of their portability, cost-effectiveness, ease of use, and ability to reliably and validly assess the outcome of interest (FAA) in adults (Hashemi et al., 2016; Krigolson et al., 2017). The Mind Monitor application (version 2.2.0) was used to record and upload the EEG recordings as discrete frequency values, through fast Fourier transform which utilize raw EEG data to calculate them. The notch filter was set to 60 Hz. The discrete frequency values were recorded in CSV files where any repetitive data that suggested an error in the signal was manually removed within the alpha signals obtained from the F7 and F8 channels. FAA was calculated by subtracting average alpha values of the right frontal hemisphere (F8) from the left frontal hemisphere (F7) [F7-F8].

Depression and Anxiety: The clinical impact of the peer-led group CBT for PPD intervention was also assessed using the EPDS and GAD-7. PPD was assessed with the EPDS, a gold standard measure of PPD symptoms (Cox et al, 1987) with a high test-retest reliability (Kernot et al., 2015). It consists of ten items rated by mothers on a 0-3 point scale based on their

feelings over the past week. Higher scores on EPDS suggest worse symptoms of PPD. Cronbach's alpha for this measure was high (α=0.75).

Levels of symptoms of anxiety were assessed using the GAD-7 scale, where seven items were rated by self-report regarding the occurrence of certain symptoms the mothers experienced in the past two weeks. The items were rated from 0-3 where 0 indicated "Not at all" and 3 indicated "Nearly every day". Greater scores indicate more severe symptoms of anxiety. The Cronbach's alpha for this measure was also high in this sample (α = 0.80).

Demographic information such as maternal age, household income before tax, education (in years), infant age (in months) and sex were collected via self-report at baseline.

Statistical Analysis

Descriptive analyses were performed on demographic data where categorical variables were reported by percentage and continuous variables with means and standard deviations (SD) for each group. Differences between the experimental and the waitlist control groups at baseline were assessed using Pearson Chi-Squared test and Independent Sample T-test statistics. Predictors of loss to follow-up were examined. An intention-to-treat (ITT) approach was used where participant data is utilized without group reassignment or corrections, despite non-compliance to treatment, withdrawal or deviation from the protocol. In this manner, all follow up data were utilized and analyzed as per randomization (Gupta, 2011).

Linear mixed effect models were utilized to assess changes in the FAA and RSA data between the two time points, as well as between the two groups over time. Data were structured in a hierarchy where the outcomes from the two time points (level 1) were nested within the participants (level 2) to determine the effect of CBT over time and between groups. Within an

ITT framework with missing data, LMM conserves power as it utilizes all available data and does not use listwise deletions.

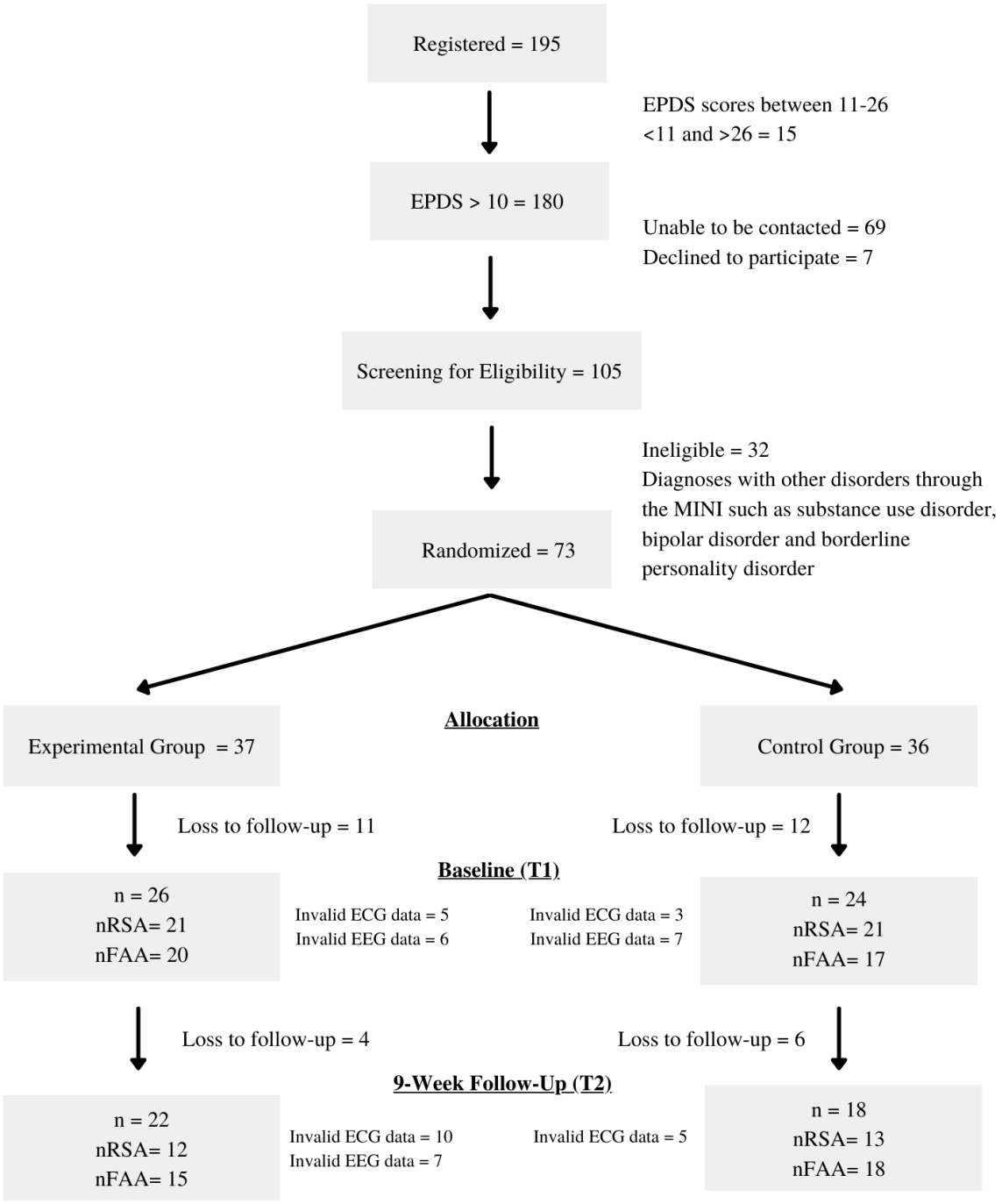
Pearson Correlation was utilized to assess the relation between the treatment outcome measures within the experimental group at baseline (T1), the 9-week follow up visit (T2) as well as the change that may have occurred between the two visits (ΔT).

Statistical analyses were conducted using the Statistical Packages for Social Sciences (SPSS) version 27 (IBM, Armonk, NY, USA). A p-value of <0.05 (two-tailed) was considered statistically significant.

Results

Sociodemographic and Clinical Data

Seventy-three participants were screened and enrolled in the present study, 36 women were allocated to the experimental group and 37 women were allocated to the control group (Figure 1). We were able to collect psychophysiological data from 26 women in the experimental group and 24 women in the control group at T1. Loss of data during analysis was either due to women choosing to discontinue the trial between study visits, issues with data collection resulting in inadequate data or corrupted files that were unable to be analyzed. Attrition between T1 and T2 in the experimental group and control group was 15% and 25% respectively. Participant characteristics at enrollment were examined as potential predictors of attrition. Within the study sample, those lost to follow-up indicated lower household income ($48,000 vs. $75,405; $t(50) = 2.81, p = 0.008$) and were younger in age (27 vs 32; $t(50) = 3.07, p = 0.004$). There were no differences in predictors of attrition between experimental and control groups.



*Invalid data includes corrupted data, inadequate data collection that rendered files unusable, and outliers (RSA>8)

Figure 1: Study design and attrition of participants over the study period

On average the participants in both groups at T1 (N=50) were in their early 30s. The mean age within the experimental group was 32.3 (SD = 4.4) while the control group was 30.2 (SD= 4.7). Majority of the mothers were white, where 4.2% within the experimental group and 4.6% within the control group were considered mixed or defined as "other" forms of ethnicity. All women in the experimental group were either in common-law relationships or married, while 10% in the control group were single or separated. Infants within the experimental group were on average 4.8 months (SD=4.2) while infants in the control group were 5.4 months (SD=3.2). Both groups had completed high school and some post-secondary education (Average years of education in the experimental group and control group was 15.2 (SD=1.5) and 14.3 years (SD=1.4) respectively). Moderate levels of depression and anxiety based on their EPDS and GAD-7 scores were reported in both groups. The MINI revealed that two-thirds of the sample met full diagnostic criteria for major depressive disorder, and a similar proportion met criteria for more than one psychiatric disorder. About one in three mothers were taking antidepressants at T1.

Table 1: Characteristics of study participants

	Experimental (N=26)		**Control (N= 24)**	
	Mean	**SD**	**Mean**	**SD**
Maternal Age (Years)	32.3	4.4	30.2	4.7
Infant Age (Months)	4.8	4.2	5.4	3.2
Maternal Education (Years)	15.2	1.5	14.3	1.4
Household Income ($)	76,818	21,906	67,000	21,788
Baseline EPDS	16.1	3.7	16.7	4.2
Baseline GAD-7	12.9	4.3	12.3	4.8

	Percent (%)	Percent (%)
Ethnicity		
White	95.8	95.2
Other	4.2	4.6
Marital Status		
Single/Separated	0	10.0
Married/Common Law	100	90.0
Infant Sex		
Male	62.5	42.9
Parity		
Primiparous	43.8	54.5
Current Diagnosis of Major Depressive Disorder	66.7	63.6
>1 Current Psychiatric Disorder	66.7	68.2
Antidepressant Use at Baseline	34.8	29.4

*T-tests and Chi-Squared Tests were performed to determine significant differences between treatment and control groups

Maternal Psychophysiological Outcomes

Differences in maternal psychophysiological outcomes from T1 to T2 in experimental and control groups were assessed using a LMM which modelled the interaction of group assignment by time (Table 2). A group by time interaction was found between T1 and T2 for HF-HRV ($F[1,63] = 4.15$, $p=0.046$). Mean HF-HRV (Table 3) decreased within the control group between T1 (M=6.21, SD= 1.05) and T2 (M=5.75, SD=1.12), but increased in the treatment group between T1 (M=6.00, SD=1.11) and T2 (M=6.66, SD=0.93). Differences in mean HF-HRV between experimental and control groups was significant at T2 ($p=0.03$). There was a large effect size change in HF-HRV between the two visits in the experimental group (Cohen d=0.70,

95% CI [0.19, 1.57]). Pearson Correlation indicated a statistically significant correlation between HF-HRV and EPDS scores (r=0.67, p=0.02), as well as GAD-7 (r=0.73, p=0.007) scores at T2.

No statistically significant difference in FAA was noted in the group by time interaction (F[1,66] = 0.05, p=0.846). Mean FAA values indicated lateralized cortical activity towards the right for the experimental group at T1 (M=0.06, SD=0.19) and T2 (M=0.01, SD=0.20). However, the control group showed a change from right to left frontal cortical lateralization between T1 (M=0.30, SD=0.20) to T2 (M=-0.31, SD=0.18), but no significant differences were found between the control and experimental group in the mean FAA values at both time points. Additional subgroup analyses were performed by using LMM to determine any group by time interaction solely on women who had greater right frontal cortical activity (FAA> 0) at T1 (N=22). There were no statistically significant interactions to show any changes towards greater left frontal EEG activity at T2 among these mothers.

A group by time interaction was also noted for EPDS scores (F[1,84] = 7.88, p=0.006). Mean EPDS scores decreased approximately five points in the experimental group from T1 (M=16.12, SD=3.80) to T2 (M=10.64, SD=4.22), and indicated a statistically significant difference compared to the control group at T2 (p=0.001). This change was clinically significant (Matthey, 2004) and the effect size was large (Cohen d=1.22, 95% CI [0.51, 1.91]). Pearson Correlation indicated statistically significant correlations between EPDS scores and GAD-7 scores at T1 (r=0.52, p=0.007), T2 (r=0.75, p<0.001) as well as the change that occurred between the two time points (r=0.51, p=0.02).

Similarly, there was a statistically significant group by time interaction for GAD-7 scores (F[1,81] = 12.46, p=0.001). A five-point decrease was indicated from T1 (M=12.60, SD=4.27) to T2 (M=7.14, SD=3.94) within the experimental group and significantly differed

from the control group at T2 (p=0.002). This change represented a large effect size (Cohen d=1.48, 95% CI [0.73, 2.21])

Table 2: Fixed effect estimates of changes in maternal physiology, depression and anxiety from T1 and T2 in experimental and waitlist control groups

Model	B	Standard error	t	p-value
Group[1] x, Time[2]				
FAA	0.0195	0.0884	0.221	0.826
HF-HRV	1.1034	0.5414	2.038	0.046*
EPDS	-5.1874	1.8483	-2.807	0.006*
GAD-7	-6.7767	1.9196	-3.530	0.001*

1. Reference = treatment group
2. Reference = T2

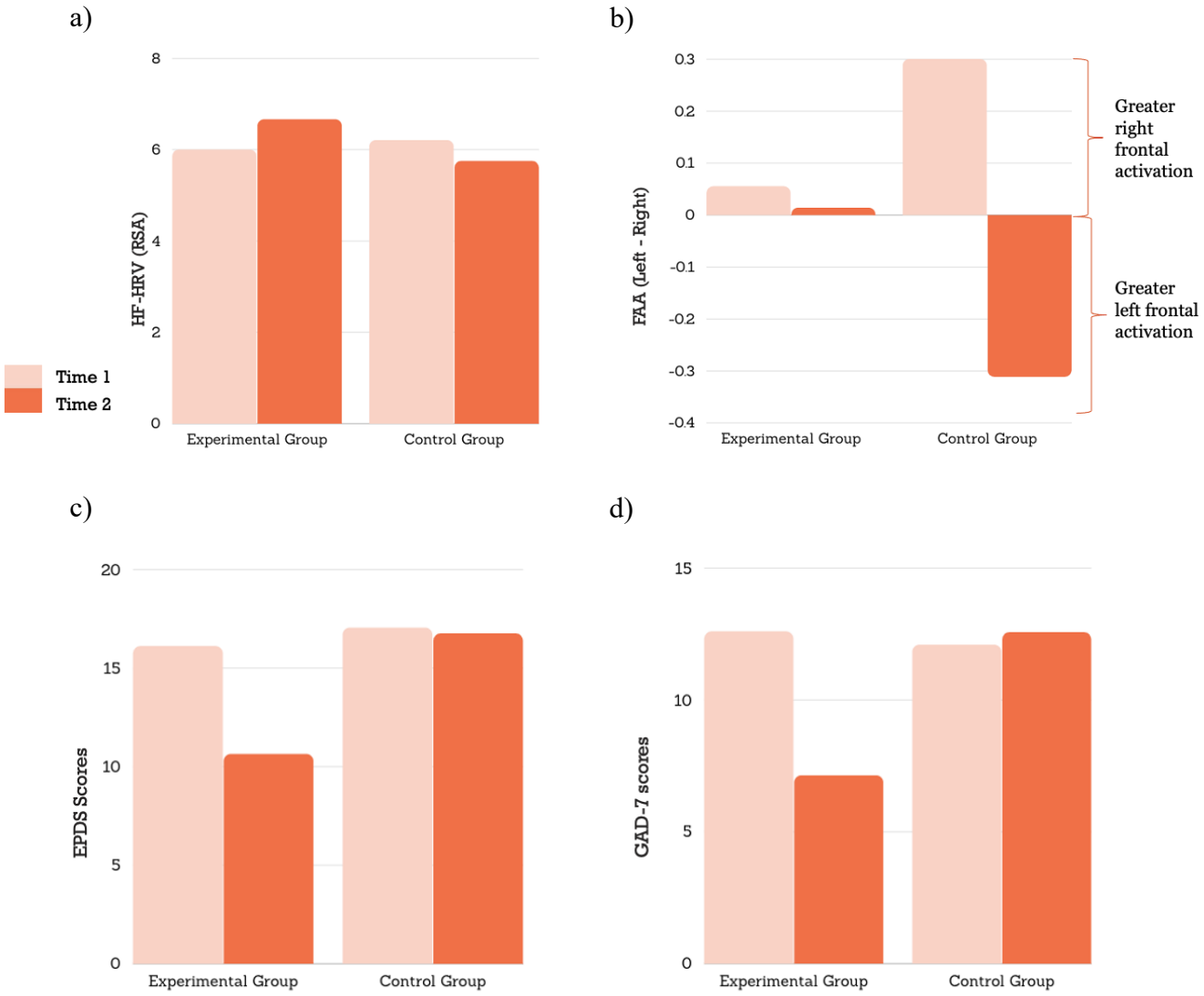


Figure 2: Mean maternal a) HF-HRV, b) FAA, c) EPDS and d) GAD-7 scores at T1 and T2 in experimental and waitlist control groups

Table 3: Maternal physiology, depression and anxiety at T1 and T2 in experimental and waitlist control groups

	N		Mean (SD)	
FAA	**T1**	**T2**	**T1**	**T2**
Control	17	18	0.300 (0.20)	-0.311 (0.18)
Treatment	20	15	0.055 (0.19)	0.014 (0.20)
HF-HRV				
Control	21	13	6.206 (1.05)	5.751 (1.12)*
Treatment	21	12	5.999 (1.11)	6.662 (0.93)*
EPDS				
Control	24	16	17.042 (4.11)	16.750 (5.18)*
Treatment	26	22	16.115 (3.80)	10.636 (4.22)*
GAD-7				
Control	23	16	12.087 (4.68)	12.563 (5.47)*
Treatment	25	22	12.600 (4.27)	7.136 (3.94)*

*T-tests were performed to determine significant differences between the means of treatment and control groups ($p<0.05$)

Table 4: Pearson correlation between the maternal physiology, depression and anxiety scores at T1, T2 and the change between study visits in the experimental group

T1	**1**	**2**	**3**	**4**
1. FAA	-			
2. **HF-HRV**	-0.177	-		
3. **EPDS**	0.153	-0.081	-	
4. **GAD-7**	0.434	-0.355	0.523*	-
T2				
1. FAA	-			
2. HF-HRV	-0.161	-		
3. EPDS	0.136	0.668*	-	
4. GAD-7	-0.151	0.731*	0.745*	-
ΔT				
1. FAA	-			
2. HF-HRV	-0.250	-		
3. EPDS	0.309	0.309	-	
4. GAD-7	-0.181	-0.181	0.514*	-

Significant correlation with $p<0.05$* (2-tailed)

Discussion

The findings from this study suggest that a nine-week group CBT intervention delivered by recovered peers leads to improvements in depression, anxiety, and HF-HRV. However, no change in FAA was observed to indicate changes in lateralization of frontal brain activity. These results suggest that the benefits of CBT may extend beyond depression and anxiety symptoms to autonomic nervous system function in mothers. Additionally, the present study indicates that the parasympathetic changes can be observed from CBT provided by peers who have recovered from PPD. This may indicate further credibility to CBT as a form of treatment to mothers with PPD by providing a non-invasive and measurable biomarker for its treatment outcome.

Past studies have not examined how the autonomic nervous system responds to treatment in mothers with PPD. However, it is consistent with the results of a study where 53 depressed outpatients received 25 sessions of individual CBT (Blanck et al., 2019). Taken together, the results of these studies suggest that CBT is capable of producing adaptive changes in HRV in adults when delivered in individual or group format and by an expert or peer therapist. While the mechanisms by which CBT influences autonomic nervous system function is not known, it may be explained by the polyvagal theory (Porges, 1995, 2001).

Polyvagal theory postulates that the ANS evolved to provide neurophysiological components for social, emotional and communicative behaviours within mammals (Porges, 2001). Immobilization (passive avoidance, behavioural shutdown) and mobilization stages (active avoidance, fight-flight behaviour) are mediated by the dorsal vagal complex (DVC) and the sympathetic-adrenal components respectively. The ventral vagal complex (VVC) is linked to social communication, self-soothing, and calming behaviours that effectively inhibits the sympathetic-adrenal components (Porges, 2001). Within the context of this present study, mothers with PPD may have benefited from CBT delivered by their peers as it allowed them to activate their VVC through increased communication, social engagement, perceived safety as well as learning strategies that increase calming behaviours. Goodyke et al (2021) further provides evidence on how perceived social support has been linked to increased HRV. This could be a mechanism by which group treatment of PPD by peers may have operated, as it may have allowed the environment to be perceived safer (Blanck et al., 2019). Therefore, vagally mediated HRV (HF-HRV) may have increased among the experimental group through the increase in the tone of VVC as a result of group CBT.

On the other hand, this study failed to show a significant group by time interaction for the FAA. It is possible that treating PPD with CBT fails to lead to changes in frontal brain activity, though the small sample size and limited duration of follow-up may also have contributed. Moreover, it may be that the use of Muse headbands played a role. However, recent literature has also highlighted inconsistencies in how the FAA is affected by treatment for depression. Van der Vinne et al. (2019) reported a lack of association in FAA and depression severity among MDD participants, as well as no significant changes in FAA when participants were treated with antidepressant medications. Furthermore, Szumska et al (2021) also examined the effects on FAA of a mindfulness-based cognitive therapy group. Mean values in FAA did not change despite improvements in depression and anxiety scores, much like the present study.

This study is the first to utilize an experimental (RCT) design to assess whether delivery of an evidence-based intervention task-shifted to peers can produce psychophysiological changes in women with PPD. Despite its use of a community-based sample, the following limitations should be noted. The small sample size, as well as the loss to follow-up between T1 and T2 reduced the statistical power available to assess putative changes occurring with treatment. Though the onset of the COVID-19 pandemic did affect our ability to follow up with some participants, future studies should attempt to recruit larger samples. The present study also contained a higher proportion of white participants who had completed high school, and all participants had access to free, universal healthcare which could reduce the generalizability of our findings. Moreover, we utilized an EPDS cut-off of 10, and about two-thirds of our sample met diagnostic criteria for MDD. While nearly one-third of postpartum mothers have these levels of symptoms (Meaney, 2018), it is possible that the inclusion of those with subsyndromal levels of symptoms or other disorders (e.g., GAD) may have affected our findings. The timing of the

onset of depression in participants was not known, and so it is not clear what proportion of mothers had new-onset PPD after delivery versus those who had pre-existing depression during pregnancy or before. Our use of the Muse headsets to assess FAA may also have affected our findings given that the use of just two channels in the frontal region to assess alpha wave activity may not capture the full extent of cortical activation that is taking place (as it does not cover the entire region).

In conclusion, our findings suggest that group CBT for PPD delivered by recovered peers has the potential to improve parasympathetic nervous system functioning, as well as depression and anxiety in a community-based sample. Further research should be conducted to address our study limitations to provide a more complete understanding of the neurobiology of PPD and its response to treatment. Such research can help to provide additional biomarkers of PPD and its treatment response and enable us to improve clinical outcomes for mothers and their families.

References

Andreae, S. J., Andreae, L. J., Richman, J. S., Cherrington, A. L., & Safford, M. M. (2021). Peer-delivered Cognitive Behavioral Therapy-based Intervention Reduced Depression and Stress in Community Dwelling Adults With Diabetes and Chronic Pain: A Cluster Randomized Trial. *Annals of Behavioral Medicine*.

Beck, A. T., Steer, R. A., & Brown, G. K. (1996). Beck depression inventory (BDI-II) (Vol. 10, p. s15327752jpa6703_13). Pearson.

Blanck, P., Stoffel, M., Bents, H., Ditzen, B., & Mander, J. (2019). Heart Rate Variability in Individual Psychotherapy: Associations With Alliance and Outcome. *The Journal of nervous and mental disease*, *207*(6), 451–458. https://doi.org/10.1097/NMD.0000000000000994

Buckwalter, J. G., Stanczyk, F. Z., McCleary, C. A., Bluestein, B. W., Buckwalter, D. K., Rankin, K. P., Chang, L., & Goodwin, T. M. (1999). Pregnancy, the postpartum, and steroid hormones: effects on cognition and mood. Psychoneuroendocrinology, 24(1), 69–84. https://doi.org/10.1016/s0306-4530(98)00044-4

Campbell SB, Cohn JF. 1997. The timing and chronicity of postpartum depression: implications for infant development. In Postpartum Depression and Child Development, ed. P Cooper, L Murray, pp. 165–97. NewYork: Guilford

Deldin, P. J., & Chiu, P. (2005). *Cognitive restructuring and EEG in major depression*. https://doi.org/10.1016/j.biopsycho.2005.01.003

Demaree, H. A., Everhart, D. E., Youngstrom, E. A., & Harrison, D. W. (2005). Brain Lateralization of Emotional Processing: Historical Roots and a Future Incorporating "Dominance." *Behavioral and Cognitive Neuroscience Reviews*, *4*(1), 3–20. https://doi.org/10.1177/1534582305276837

Dennis, C.L. (2010). Postpartum depression peer support: Maternal perceptions from a randomized controlled trial §. *International Journal of Nursing Studies*, *47*, 560–568. https://doi.org/10.1016/j.ijnurstu.2009.10.015

Field, T. (2017). *Prenatal Depression Risk Factors, Developmental Effects and Interventions: A Review*. https://doi.org/10.4172/2376-127X.1000301

Gaynes, B. N., Gavin, N., Meltzer-Brody, S., Lohr, K. N., Swinson, T., Gartlehner, G., Brody, S., & Miller, W. C. (2005). Perinatal depression: prevalence, screening accuracy, and screening outcomes. *Evidence report/technology assessment (Summary)*, (119), 1–8. https://doi.org/10.1037/e439372005-001

Gold, C., Fachner, J., & Erkkilä, J. (2013). Validity and reliability of electroencephalographic frontal alpha asymmetry and frontal midline theta as biomarkers for depression. *Scandinavian Journal of Psychology*, *54*(2), 118–126. https://doi.org/10.1111/sjop.12022

Goodyke, M. P., Hershberger, P. E., Bronas, U. G., & Dunn, S. L. (2021). Perceived Social Support and Heart Rate Variability: An Integrative Review. Western Journal of Nursing Research. https://doi.org/10.1177/01939459211028908

Guintivano, J., Manuck, T., & Meltzer-Brody, S. (2018). Predictors of Postpartum Depression: A Comprehensive Review of the Last Decade of Evidence. *Clinical Obstetrics and Gynecology*, *61*(3), 591–603. https://doi.org/10.1097/GRF.0000000000000368

Gupta S. K. (2011). Intention-to-treat concept: A review. *Perspectives in clinical research*, *2*(3), 109–112. https://doi.org/10.4103/2229-3485.83221

Hartmann, R., Schmidt, F. M., Sander, C., & Hegerl, U. (2019). Heart rate variability as indicator of clinical state in depression. *Frontiers in Psychiatry*, *10*(JAN). https://doi.org/10.3389/fpsyt.2018.00735

Hashemi, A., Pino, L. J., Moffat, G., Mathewson, K. J., Aimone, C., Bennett, P. J., Schmidt, L. A., & Sekuler, A. B. (2016). Characterizing Population EEG Dynamics throughout Adulthood. *eNeuro*, *3*(6), ENEURO.0275-16.2016. https://doi.org/10.1523/ENEURO.0275-16.2016

Henriques, J. B., & Davidson, R. J. (1990). Regional brain electrical asymmetries discriminate between previously depressed and healthy control subjects. Journal of Abnormal Psychology, 99(1), 22–31. https://doi.org/10.1037/0021-843X.99.1.22

Hernán, M. A., Hernández-Díaz, S., & Robins, J. M. (2004). A structural approach to selection bias. *Epidemiology (Cambridge, Mass.)*, *15*(5), 615–625. https://doi.org/10.1097/01.ede.0000135174.63482.43

Huang, R., Yan, C., Tian, Y., Lei, B., Yang, D., Liu, D., & Lei, J. (2020). *Effectiveness of peer support intervention on perinatal depression: A systematic review and meta-analysis*. https://doi.org/10.1016/j.jad.2020.06.048

IBM Corp. Released 2020. IBM SPSS Statistics for Windows, Version 27.0. Armonk, NY: IBM Corp

Izumi, M., Manabe, E., Uematsu, S., Watanabe, A., & Moritani, T. (2016). Autonomic nervous system activity and anxiety and depressive symptoms in mothers up to 2 years

postpartum. *J Psychosom Obstet Gynaecol*, 1743–8942. https://doi.org/10.3109/0167482X.2016.1142970

Josefsson, A., Berg, G., Nordin, C., & Sydsjö, G. (2001). Prevalence of depressive symptoms in late pregnancy and postpartum. Acta Obstetricia et Gynecologica Scandinavica, 80(3), 251–255. https://doi.org/10.1034/j.1600-0412.2001.080003251.x

Kernot, J., Olds, T., Lewis, L.K. *et al.* Test-retest reliability of the English version of the Edinburgh Postnatal Depression Scale. *Arch Womens Ment Health* 18, 255–257 (2015). https://doi.org/10.1007/s00737-014-0461-4

Krause, D., Jobst, A., Kirchberg, F., Kieper, S., Härtl, K., Kästner, R., Myint, A. M., Müller, N., & Schwarz, M. J. (2014). Prenatal immunologic predictors of postpartum depressive symptoms: a prospective study for potential diagnostic markers. European archives of psychiatry and clinical neuroscience, 264(7), 615–624. https://doi.org/10.1007/s00406-014-0494-8

Krigolson, O. E., Williams, C. C., Norton, A., Hassall, C. D., & Colino, F. L. (2017). Choosing MUSE: Validation of a Low-Cost, Portable EEG System for ERP Research. *Frontiers in neuroscience*, *11*, 109. https://doi.org/10.3389/fnins.2017.00109

Levis, B., Negeri, Z., Sun, Y., Benedetti, A., & Thombs, B. D. (2020). Accuracy of the Edinburgh Postnatal Depression Scale (EPDS) for screening to detect major depression among pregnant and postpartum women: systematic review and meta-analysis of individual participant data. *BMJ*, m4022. https://doi.org/10.1136/bmj.m4022

Matthey S. (2004). Calculating clinically significant change in postnatal depression studies using the Edinburgh Postnatal Depression Scale. *Journal of affective disorders*, *78*(3), 269–272. https://doi.org/10.1016/S0165-0327(02)00313-0

Meaney M. J. (2018). Perinatal Maternal Depressive Symptoms as an Issue for Population Health. *The American journal of psychiatry*, *175*(11), 1084–1093. https://doi.org/10.1176/appi.ajp.2018.17091031

Milgrom, J., Negri, L. M., Gemmill, A. W., McNeil, M., & Martin, P. R. (2005). A randomized controlled trial of psychological interventions for postnatal depression. *British Journal of Clinical Psychology*, *44*(4), 529–542. https://doi.org/10.1348/014466505X34200

Payne, J. L., & Maguire, J. (2019). Pathophysiological mechanisms implicated in postpartum depression. *Frontiers in Neuroendocrinology*, *52*, 165–180. https://doi.org/10.1016/j.yfrne.2018.12.001

Porges S. W. (1995). Orienting in a defensive world: mammalian modifications of our evolutionary heritage. A Polyvagal Theory. *Psychophysiology*, *32*(4), 301–318. https://doi.org/10.1111/j.1469-8986.1995.tb01213.x

Porges, S. W. (2001). The polyvagal theory: Phylogenetic substrates of a social nervous system. *International Journal of Psychophysiology, 42*(2), 123–146. https://doi.org/10.1016/S0167-8760(01)00162-3

Porges S. W. (2007). The polyvagal perspective. *Biological psychology*, *74*(2), 116–143. https://doi.org/10.1016/j.biopsycho.2006.06.009

Prevatt, B.-S. L. E. M. . D. S. L. (2018). *Peer-support intervention for postpartum depression: Participant satisfaction and program effectiveness*. https://doi.org/10.1016/j.midw.2018.05.009

Rottenberg, J., Clift, A., Bolden, S., & Salomon, K. (2007). RSA fluctuation in major depressive disorder. *Psychophysiology*, *44*(3), 450–458. https://doi.org/10.1111/j.1469-8986.2007.00509.x

Scope, A., Leaviss, J., Kaltenthaler, E., Parry, G., Sutcliffe, P., Bradburn, M., & Cantrell, A. (2013). *Is group cognitive behaviour therapy for postnatal depression evidence-based practice? A systematic review*. http://www.biomedcentral.com/1471-244X/13/321

Segrave, R. A., Cooper, N. R., Thomson, R. H., Croft, R. J., Sheppard, D. M., & Fitzgerald, P. B. (2011). Individualized alpha activity and frontal asymmetry in major depression. *Clinical EEG and neuroscience*, *42*(1), 45–52.

Shaffer, F., & Ginsberg, J. P. (2017). An Overview of Heart Rate Variability Metrics and Norms. *Frontiers in Public Health*, *5*(September), 1–17. https://doi.org/10.3389/fpubh.2017.00258

Simpson, W., Glazer, M., Michalski, N., Steiner, M., & Frey, B. N. (2014). Comparative efficacy of the generalized anxiety disorder 7-item scale and the Edinburgh Postnatal Depression Scale as screening tools for generalized anxiety disorder in pregnancy and the postpartum period. *Canadian Journal of Psychiatry*, *59*(8), 434–440. https://doi.org/10.1177/07067431405900806

Sockol, L. E. (2015). A systematic review of the efficacy of cognitive behavioral therapy for treating and preventing perinatal depression. *Journal of Affective Disorders*, *177*, 7–21. https://doi.org/10.1016/j.jad.2015.01.052

Spitzer RL, Kroenke K, Williams JBW, Löwe B. A Brief Measure for Assessing Generalized Anxiety Disorder: The GAD-7. Arch Intern Med. 2006;166(10):1092–1097. doi:10.1001/archinte.166.10.1092

Stewart, D. E., & Vigod, S. N. (2019). Annual Review of Medicine Postpartum Depression: Pathophysiology, Treatment, and Emerging Therapeutics. *Annu. Rev. Med. 2019*, *70*, 183–196. https://doi.org/10.1146/annurev-med-041217

Szumska, I., Gola, M., Rusanowska, M., Krajewska, M., Żygierewicz, J., Krejtz, I., Nezlek, J. B., & Holas, P. (2020). Mindfulness-based cognitive therapy reduces clinical symptoms, but do not change frontal alpha asymmetry in people with major depression disorder. *International Journal of Neuroscience*, *131*(5), 453–461. https://doi.org/10.1080/00207454.2020.1748621

Thayer, J. F., & Lane, R. D. (2007). The role of vagal function in the risk for cardiovascular disease and mortality. *Biological psychology*, *74*(2), 224–242. https://doi.org/10.1016/j.biopsycho.2005.11.013

Tucker, M., & Oei, T. (2007). Is Group More Cost Effective than Individual Cognitive Behaviour Therapy? The Evidence is not Solid Yet. *Behavioural and Cognitive Psychotherapy, 35*(1), 77-91. doi:10.1017/S1352465806003134

van der Vinne, N., Vollebregt, M. A., van Putten, M. J. A. M., & Arns, M. (2017). Frontal alpha asymmetry as a diagnostic marker in depression: Fact or fiction? A meta-analysis. *NeuroImage: Clinical*, *16*(April), 79–87. https://doi.org/10.1016/j.nicl.2017.07.006

Van Lieshout, R. J., Yang, L., Haber, E., & Ferro, M. A. (2017). Evaluating the effectiveness of a brief group cognitive behavioural therapy intervention for perinatal depression. *Archives of Women's Mental Health*, *20*(1), 225–228. https://doi.org/10.1007/s00737-016-0666-9

Van Lieshout, R. J. (2018, January). Peer Administered CBT for PPD. *Identifier NCT03285139*. https://clinicaltrials.gov/ct2/show/study/NCT03285139

Wen, D., Soe, N., Sim, L. et al. Infant frontal EEG asymmetry in relation with postnatal maternal depression and parenting behavior. Transl Psychiatry 7, e1057 (2017). https://doi.org/10.1038/tp.2017.28

Yim, I. S., Tanner Stapleton, L. R., Guardino, C. M., Hahn-Holbrook, J., & Dunkel Schetter, C. (2015). Biological and psychosocial predictors of postpartum depression: systematic review and call for integration. *Annual review of clinical psychology*, *11*, 99–137. https://doi.org/10.1146/annurev-clinpsy-101414-02042645xsd